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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,557	12/22/2003	Khalid K. Sadozai	1767.2011-000	5063

21005 7590 10/03/2007

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
BROWN, COURTNEY A	

ART UNIT	PAPER NUMBER
1609	

MAIL DATE	DELIVERY MODE
10/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/743,557	SADOZAI ET AL.	
	Examiner	Art Unit	
	Courtney A. Brown	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 23-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/21/2004 and 9/30/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10, drawn to a hyaluonic acid (HA) composition comprising crosslinked, water-insoluble, hydrated HA gel particles, wherein the HA includes crosslinks represented by the formula: HA'-U-R_2-U-HA'

II. Claims 11-22, drawn to a method of augmenting tissue in a subject that is in need of tissue agumentation comprising inserting a needle into a subject loaded with a crosslinked HA composition and applying force to the syringe, whereby at least a portion of the HA composition is delivered into the subject.

III. Claims 23-31, drawn to a method of preparing a HA composition comprising :

a.) forming water-insoluble, dehydrated cross-linked HA particles;

b.) separating the water-insoluble, dehydrates particles by average diameter and selecting a subset of particles by average diameter;

c.) hydrating the subset of dehydrated particles with a physiologically compatible aqueous solution, thereby forming the HA composition.

IV. Claims, 32-37, drawn to a method of preparing a crosslinked HA composition comprising the steps of :

a.) crosslinking a precursor of the crosslinked HA with a biscarbodiimide in the presence of a pH buffer, wherein the resulting crosslinked HA includes crosslinks represented by the following formula: HA'-U-R_2U-HA' and

b.) dehydrating the crosslinked HA to produce the dehydrated, crosslinked HA.

V. Claims 38-41, drawn to a stabilized HA composition comprising crosslinked HA and at least about 0.1% by weight of a local anesthetic, wherein the value of storage modulus G' for the stabilized composition is at least about 110% of the value f G' measured for a non-stabilized composition, when measured at 37 °C and 1 Hz frequency using a 4 cm flat geometry.

VI. Claims 42- 46, drawn to a method of stabilizing crosslinked HA, comprising hydrating water-insoluble, dehydrated crosslinkd HA with a physiologically compatible aqueous solution, thereby forming the stabilized HA composition, wherein the physiologically compatible aqueous solution includes at least about 110% of the value f G' measured for a non-stabilized composition, when measured at 37 °C and 1 Hz frequency using a 4 cm flat geometry.

VII. Claims 47-48, drawn to a HA compositon comprising crosslinked, water-insoluble hydrated HA gel particles, wherein:

a.) the particles include lidocaine HCl

b.) the particles have an average diameter selected from the group consisting of a hydrated particle average diameter between about 20 and about 1000 μm, and a dehydrated particle average diameter between about 10 and about 500μm;

c.) the particles include crosslinks represented by the following formula: HA'-U-R_2U-HA'

d.) the composition has at least one parameter measured at 37 °C selected from a storage modulus G' of at least about 50 Pa when measured at 1 Hz frequency using a 4 cm flat geometry, and a kinematic viscosity of at least about 20,000 cPs when measured at a shear rate of $1s^{-1}$; and

e.) the composition is sufficiently stable to enzymatic degradation that upon combining the composition at 37 °C with hyaluronidase enzyme in an amount of abou 0.3% by weight, under conditions suitable for reaction with hyaluronidase.

The inventions are distinct, each from the other because of the following reasons:

Inventions I,V, and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, Group I requires crosslinked, water-insoluble, hydrated HA gel particles represented by the formula: HA'-U-R_2-U-HA'. Group V requires a stabilized HA composition comprising crosslinked HA and at least about 0.1% by weight of a local anesthetic, wherein the value of storage modulus G' for the stabilized composition is at least about

110% of the value f G' measured for a non-stabilized composition, when measured at 37 °C and 1 Hz frequency using a 4 cm flat geometry. Group VII requires crosslinked, water-insoluble hydrated HA gel particles, wherein the particles include lidocaine HCl.

Inventions III,IV and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, Groups III, IV, and VI are independent and distinct from each other as they are drawn to different methods of making or preparing a HA composition.

Inventions I,V,VII and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the process for using the product as claimed can be practiced with another materially different product. For example, mammal tissue could be augmented by injecting compositions comprising a biocompatible ceramic matrix in an acceptable fluid carrier that contains a calcium phosphite mineral. (see EP 627899 B1).

Because these inventions are distinct for the reasons given above and the search required for group I is not required for groups II-VII, restriction for examination

purposes as indicated is proper. Groups I-VII are not identically classified under U.S. Patent Classification guidelines, thus, to search them together would present a search burden on the Examiner. Moreover, the searches in non-patent literature databases are extensive and do not overlap thus presenting a search burden to be searched together. Thus, groups I-IV have been appropriately restricted on the basis of being both independent or distinct and presenting a search burden on the Examiner if they were to be searched together.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with N. Scott Pierce on September 22, 2007 a provisional election was made with traverse to prosecute the invention of group II, claims 11-22. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-10 and 23-48 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Objections

The abstract of the disclosure is objected to because it is more than one paragraph and more than 25 lines. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadozai et al. (WO 02/09792 A1) in view of Naughton et al. (US 6372494 B1) .

Applicant's Invention

Applicant claims a hyaluronic acid composition that includes cross-linked, water-insoluble hydrated hyaluronic acid gel particles. These particles have a preferred diameter between about 20 μm to about 1000 μm wherein the distribution of the said particles is a multimodial distribution. The cross linkage of the particle may be

performed with different compounds such an optionally substituted O-acyl isourea or N-acyl urea. The said composition may further comprise a local anesthetic, specifically lidocaine HCl. Additionally, the said composition may be used in the field of tissue augmentation in which it is administered by forceful needle injection into a human at the location needing tissue augmentation.

Determination of the scope and the content of the prior art

(MPEP 2141.01)

In reference to claims 11-16 of the instant application Sadozai et al. discloses composites including a biocompatible and biodegradable support comprising a water-insoluble hyaluronic acid derivative that includes an N-acyl urea that results from cross-linking (see abstract). On page 4, lines 2-3, this reference teaches a drug delivery system which can be easily injected or implanted. Additionally, this reference teaches that the composition can be administered to humans (page 19, lines 9-10) and injected or implanted at the locus where delivery is desired (page 16, lines 10-11).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Sadozai et al. do not teach a composition that further comprises a local anesthetic, specifically lidocaine HCl.

Naughton et al. teach, in column 22 lines 66-67 to column 23 lines 1-4, wound healing application that uses modified, cross-linked hyaluronic acids. In column 26,

lines 13-24 and 35-37, Naughton et al. teach an injectable embodiment, dispensed from syringes, for dermal augmentation and the use of lidocaine and hyaluronic acid.

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant application to combine the teachings of Sadozai et al. Naughton et al., to devise a hyaluronic acid composition that comprises cross linked (performed with O-acyl isourea or N-acyl urea), water-insoluble hydrated hyaluronic acid gel particles and lidocaine. A local anesthetic such as lidocaine is usually added with injections to reduce local pain upon injection.

Claims 11-12 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadozai et al. (WO 02/09792 A1) in view of Radice etal(US 6699471 B2) and further in view of), Szoka (US 6593308 B2), Toreki et al. (US 2002/0050659).

Determination of the scope and the content of the prior art

(MPEP 2141.01)

In reference to claims 11-12 and 17-18 of the instant application Sadozai et al. discloses composites including a biocompatible and biodegradable support comprising a water-insoluble hyaluronic acid derivative that includes an N-acyl urea that results from cross-linking (see abstract). On page 4, lines 2-3, this references teach a drug delivery system which can be easily injected or implanted. Additionally, this reference

teaches that the composition can be administered to humans (page 19, lines 9-10) and injected or implanted at the locus where delivery is desired (page 16, lines 10-11).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Sadozai et al. does not teach a composition that includes cross-linked, water-insoluble, hydrated hyaluronic acid gel particles with a diameter between 20 μm to about 1000 μm wherein the distribution of the said particles is a multimodial distribution.

Toreki et al. teach the use of hydrated gel particles as a method to encapsulate liquids (see column 17). In claim 22, this reference discloses hydrocapsules ranging from 100 to 25,000 micometers.

Szoka teach a drug delivery system vehicle having a low molecular weight hyaluronan (hyaluronic acid) ligand. In reference to claim 18 of the instant application, this reference teach the use of a multimodal program with a monodisperse particle size distribution (column 16, lines 22-26).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant application to combine the teachings of Sadozai et al., Toreki et al., and Szoka to devise a composition that includes cross-linked, water-insoluble, hydrated

hyaluronic acid gel particles with a diameter between 20 µm to about 1000 µm wherein the distribution of the said particles is a multimodial distribution. The use of hyaluronic acid for this invention is important because it is a major component of skin, where it is involved in tissue repair. In 2003 the FDA approved hyaluronan (hyaluronic acid) injections for filling soft tissue defects under the trade name Restylane. Since this composition is injected through a syringe, the size and distribution of the gel particles are important. With multimodal distribution there is continuous probability distribution of the particles at the augmentation site. For a patient undergoing a cosmetic procedure to fill in a wrinkle (tissue augmentation), it is important that the particles evenly distribute.

Claims 11-12 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadozai et al. (WO 02/09792 A1) in view of Radice al., (US 6699471 B2).

Determination of the scope and the content of the prior art

(MPEP 2141.01)

In reference to claims 11-12 and 19-22 of the instant application Sadozai et al. discloses composites including a biocompatible and biodegradable support comprising a water-insoluble hyaluronic acid derivative that includes an N-acyl urea that results from cross-linking (see abstract). On page 4, lines 2-3, this reference teaches a drug delivery system which can be easily injected or implanted. Additionally, this reference teaches that the composition can be administered to humans (page 19, lines 9-10) and injected or implanted at the locus where delivery is desired (page 16, lines 10-11).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Sadozai et al. do not teach a composition that includes cross-linked, water-insoluble, hydrated hyaluronic acid gel particles with at least one parameter measured at 37° C selected from a storage modulus G' of at least about 400 Pa when measured at 1 Hz frequency using a 4 cm flat geometry, and a kinematic viscosity of at least about 200, cPs when measured at a shear rate of $1s^{-1}$.

Radice et al. teach the use of injectable hyaluronic acid derivatives (abstract). In relation to the instant application, this reference teaches when prepared in the form of gels, crossed-linked derivatives of hyaluronic acid have greater viscosity than that of unmodified hyaluronic acid. This reference teaches that the most preferred are those gels having a viscosity of at least 350 or 400 $Pa*sec^{-1}$ (column 10, lines 47-56).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant application to combine the teachings of Sadozai et al. and Radice et al. to devise a composition that includes cross-linked, water-insoluble, hydrated hyaluronic acid gel particles with at least one parameter measured at 37° C selected from a

storage modulus G' of at least about 400 Pa when measured at 1 Hz frequency using a 4 cm flat geometry, and a kinematic viscosity of at least about 200, cPs when measured at a shear rate of $1s^{-1}$. By controlling the viscosity, both degradation time and affect on adhesion prevention can be varied. This is important because it is related to duration of the injection given for the cosmetic augmentation procedure.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR Only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electron Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Courtney Brown, whose telephone number is 571-270-3284. The examiner can normally be reached on Monday-Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number

for the organization where this application or proceeding is assigned is 571-273-8300.

Courtney A. Brown

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER